AFRL-AFOSR-VA-TR-2015-0298

Understanding Synchrony and Stochasticity in Coupled Neuronal and Genetic Oscillators

Daniel Forger
UNIVERSITY OF MICHIGAN

09/01/2015
Final Report

Air Force Research Laboratory
AF Office Of Scientific Research (AFOSR)/ RTB2
Arlington, Virginia 22203
Air Force Materiel Command

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ORGANIZATION.

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
31-08-2015	Final Report	From 1 - 6 - 2014 To 31 - 5- 2015

4. TITLE AND SUBTITLE

Understanding Synchrony and Stochasticity in Coupled Neuronal and Genetic Oscillators

5a. CONTRACT NUMBER

5b. GRANT NUMBER

FA 9550-14-1-0092

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Daniel B Forger

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The Regents of the University of Michigan
3003 S. State Street
Ann Arbor, MI 48109-1274

8. PERFORMING ORGANIZATION REPORT NUMBER

F035146

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

USAF, AFRL DUNS 143574726
AF OFFICE OF SCIENTIFIC RESEARCH
875 NORTH RANDOLPH STREET, RM 3112
ARLINGTON VA 22203

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Unlimited/Full Public Distribution

DISTRIBUTION A: Distribution approved for public release.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Coupled biological oscillators form the basis of much decision making in humans as well as the animal world. Oscillations typically occur biochemically within a cell, or through cell signals using changes in the cells electrical activity. Here, we seek to understand these processes using mathematical modeling. The work is computational, but based on careful consideration of biological data. This allows us to derive general principles that can be widely applied to many systems, both biological and non-biological. Our work also uses cutting edge computational techniques, which also can be widely applied. Our original proposal of two years was cut to one. Nevertheless, we have made extraordinary progress on the aims of the grant. Two papers have been published in PNAS. Additionally, another paper has appeared, and two more are in progress.

15. SUBJECT TERMS

Information Processing, Sensory Systems, Mathematical Modeling

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Daniel B Forger
					19b. TELEPHONE NUMBER *(Include area code)* 734-763-4544

Reset

Standard Form 298 (Rev. 8/98)
Prescribed by ANSI Std. Z39.18
Adobe Professional 7.0

DISTRIBUTION A: Distribution approved for public release.

INSTRUCTIONS FOR COMPLETING SF 298

1. REPORT DATE. Full publication date, including day, month, if available. Must cite at least the year and be Year 2000 compliant, e.g. 30-06-1998; xx-06-1998; xx-xx-1998.

2. REPORT TYPE. State the type of report, such as final, technical, interim, memorandum, master's thesis, progress, quarterly, research, special, group study, etc.

3. DATES COVERED. Indicate the time during which the work was performed and the report was written, e.g., Jun 1997 - Jun 1998; 1-10 Jun 1996; May - Nov 1998; Nov 1998.

4. TITLE. Enter title and subtitle with volume number and part number, if applicable. On classified documents, enter the title classification in parentheses.

5a. CONTRACT NUMBER. Enter all contract numbers as they appear in the report, e.g. F33615-86-C-5169.

5b. GRANT NUMBER. Enter all grant numbers as they appear in the report, e.g. AFOSR-82-1234.

5c. PROGRAM ELEMENT NUMBER. Enter all program element numbers as they appear in the report, e.g. 61101A.

5d. PROJECT NUMBER. Enter all project numbers as they appear in the report, e.g. 1F665702D1257; ILIR.

5e. TASK NUMBER. Enter all task numbers as they appear in the report, e.g. 05; RF0330201; T4112.

5f. WORK UNIT NUMBER. Enter all work unit numbers as they appear in the report, e.g. 001; AFAPL30480105.

6. AUTHOR(S). Enter name(s) of person(s) responsible for writing the report, performing the research, or credited with the content of the report. The form of entry is the last name, first name, middle initial, and additional qualifiers separated by commas, e.g. Smith, Richard, J, Jr.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES). Self-explanatory.

8. PERFORMING ORGANIZATION REPORT NUMBER. Enter all unique alphanumeric report numbers assigned by the performing organization, e.g. BRL-1234; AFWL-TR-85-4017-Vol-21-PT-2.

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES). Enter the name and address of the organization(s) financially responsible for and monitoring the work.

10. SPONSOR/MONITOR'S ACRONYM(S). Enter, if available, e.g. BRL, ARDEC, NADC.

11. SPONSOR/MONITOR'S REPORT NUMBER(S). Enter report number as assigned by the sponsoring/ monitoring agency, if available, e.g. BRL-TR-829; -215.

12. DISTRIBUTION/AVAILABILITY STATEMENT. Use agency-mandated availability statements to indicate the public availability or distribution limitations of the report. If additional limitations/ restrictions or special markings are indicated, follow agency authorization procedures, e.g. RD/FRD, PROPIN, ITAR, etc. Include copyright information.

13. SUPPLEMENTARY NOTES. Enter information not included elsewhere such as: prepared in cooperation with; translation of; report supersedes; old edition number, etc.

14. ABSTRACT. A brief (approximately 200 words) factual summary of the most significant information.

15. SUBJECT TERMS. Key words or phrases identifying major concepts in the report.

16. SECURITY CLASSIFICATION. Enter security classification in accordance with security classification regulations, e.g. U, C, S, etc. If this form contains classified information, stamp classification level on the top and bottom of this page.

17. LIMITATION OF ABSTRACT. This block must be completed to assign a distribution limitation to the abstract. Enter UU (Unclassified Unlimited) or SAR (Same as Report). An entry in this block is necessary if the abstract is to be limited.

Grant Title: Understanding Synchrony and Stochasticity in Coupled Neuronal and Genetic Oscillators

Grant #: FA 9550-14-1-0092

Reporting Period: 6/1/2014-5/31/2015

Program Manager: Patrick Bradshaw

PI: Daniel Forger, University of Michigan

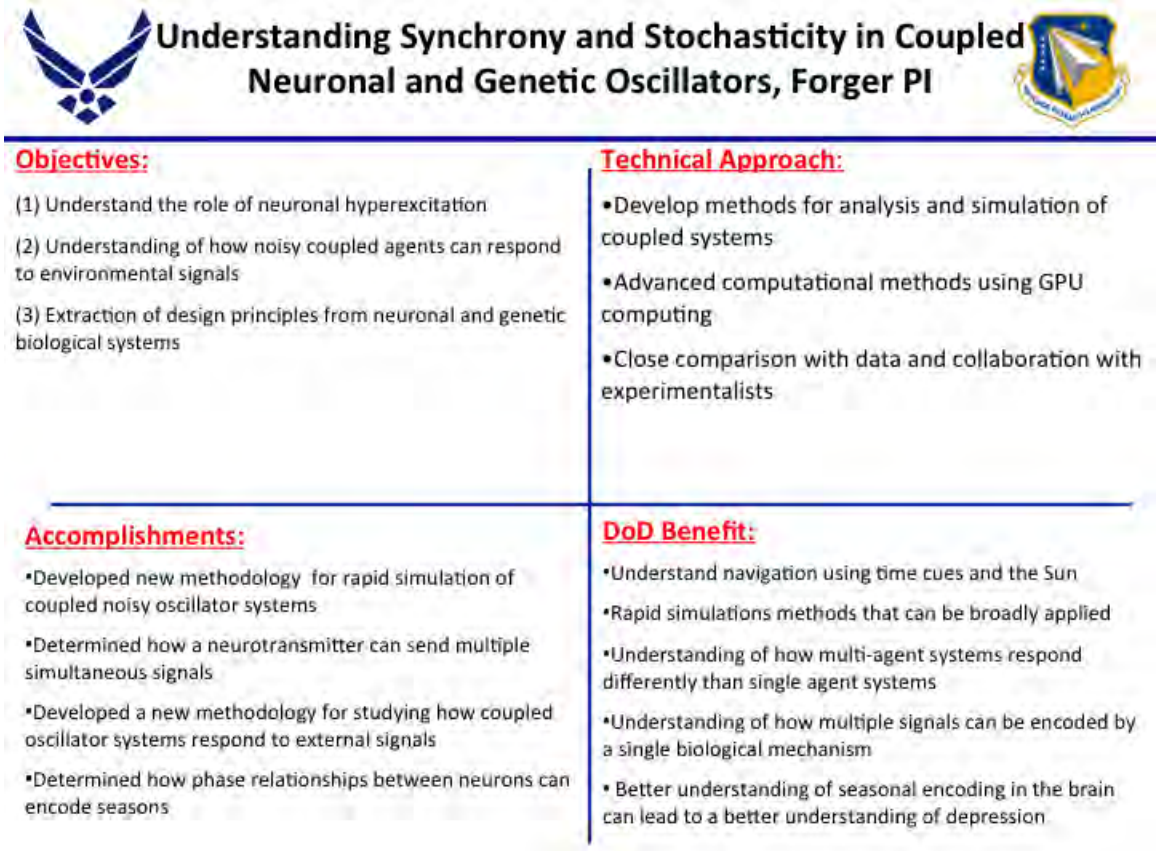
Table of Contents:

Overview: Coupled biological oscillators form the basis of much decision making in humans as well as the animal world. Oscillations typically occur biochemically within a cell, or through cell signals using changes in the cells electrical activity. Here, we seek to understand these processes using mathematical modeling. The work is computational, but based on careful consideration of biological data. This allows us to derive general principles that can be widely applied to many systems, both biological and nonbiological. Our work also uses cutting edge computational techniques, which also can be widely applied. Our original proposal of two years was cut to one. Nevertheless, we have made extraordinary progress on the aims of the grant. Two papers have been published in PNAS. Additionally, another paper has appeared, and two more are in progress.

We have discovered how multiple signals can be simultaneously sent with the same signaling molecules. The basis for this was the hyperexcited states studied in Aim 1. We have discovered how a coupled oscillator system can be used to encode patterns of light indicating the season also based on these hyperexcited states. We have developed general principles for how a coupled oscillator system responds differently to light than if the individual elements were uncoupled. Additional work not yet published has uncovered new tools to rapidly simulate coupled noisy oscillator systems. This later work comes directly from Aim 2. Additionally, fulfilling an Air Force need, we have used our work to understand principles of monarch butterfly navigation.

We remain thankful to AFOSR for the opportunity to perform this research.

Quad Chart:



Special honors and indications of our progress: We have been invited to give several high profile talks on this work, including seminars at the University of Chicago, University of Alabama at Birmingham, the World Congress of Chronobiology, Shanghai Jiao Tong University. Our two PNAS papers were featured in a review in Science Signaling.

Broader Interactions with the Air Force: We were happy to travel to a meeting organized by this AFOSR program outside of Eglin AFB and received much positive feedback from our talk. Moreover, we were asked to provide support for an AFOSR project headed by Steve Reppert on monarch butterfly navigation. This work is detailed in Schilerman et al. This shows how our work is directly relevant for the Air Force mission.

Publication and Dissemination of Results: Since the majority of our work is now, or will soon be publically available, we will simply summarize these results, and, as is standard for final reports, point the reader to the publications for details. We will describe in further depth work that we have performed which is not published. For this reason, we provide a summary of our published results below, and point the reader to the full reports.

Summary of DeWoskin D, Myung J, Belle MD, Piggins HD, Takumi T and Forger DB "Distinct roles for GABA across multiple timescales in mammalian circadian timekeeping" *PNAS* 112 (2015) E3911-9.

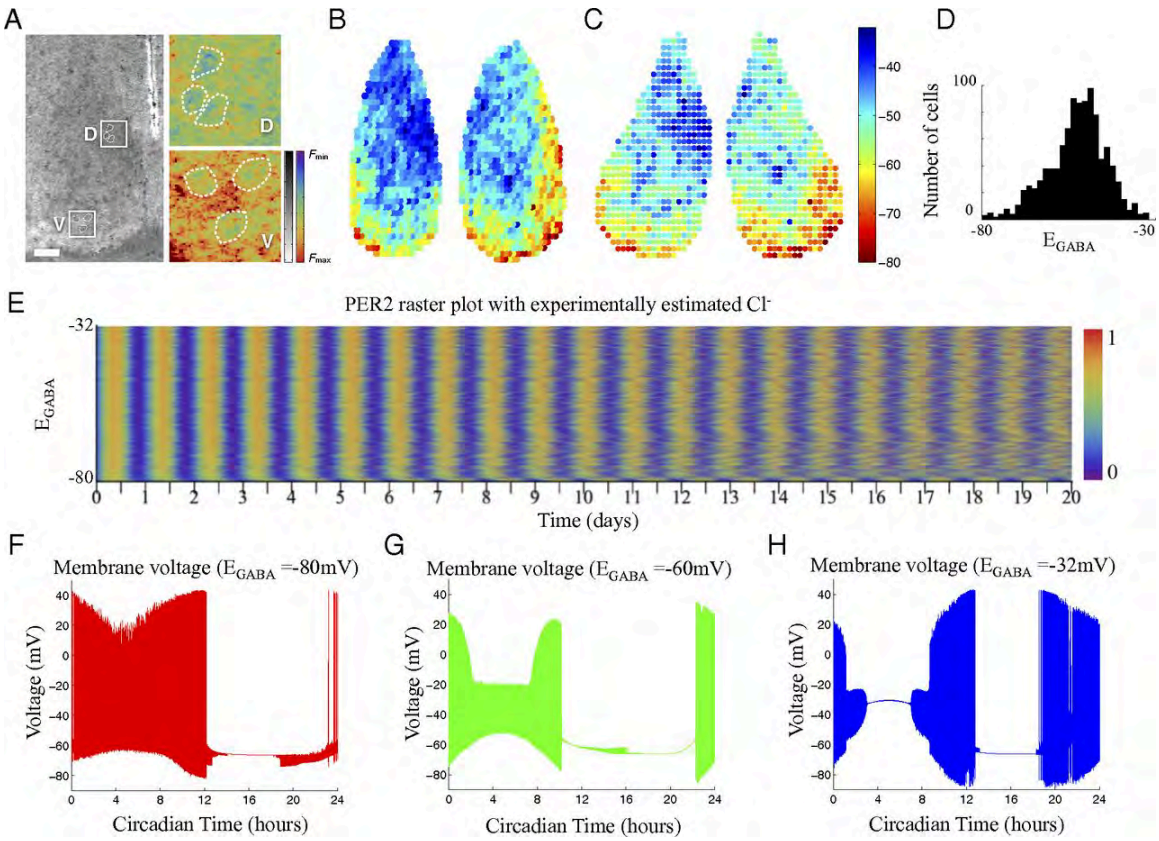
Summary from paper:

Each day, over 50 billion synaptic signals, mediated by the neurotransmitter GABA, are sent between neurons in the central circadian pacemaker in the mammalian brain to time and coordinate daily events. Although GABA is the only signaling molecule sent and received by most, if not all of these neurons, its role is not well understood. Past studies have shown paradoxically that GABA can synchronize and desynchronize, as well as excite and inhibit, clock neurons. Through experiments and modeling characterizing the role of GABA in timekeeping, we propose the existence of two types of differentially regulated GABA signaling—fast signaling that regulates neuronal output, and slow signaling that modulates synchrony between neurons—a hypothesis that can explain many previous experimental results.

The suprachiasmatic nuclei (SCN), the central circadian pacemakers in mammals, comprise a multiscale neuronal system that times daily events. We use recent advances in graphics processing unit computing to generate a multiscale model for the SCN that resolves cellular electrical activity down to the timescale of individual action potentials and the intracellular molecular events that generate circadian rhythms. We use the model to study the role of the neurotransmitter GABA in synchronizing circadian rhythms among individual SCN neurons, a topic of much

debate in the circadian community. The model predicts that GABA signaling has two components: phasic (fast) and tonic (slow). Phasic GABA postsynaptic currents are released after action potentials, and can both increase or decrease firing rate, depending on their timing in the interspike interval, a modeling hypothesis we experimentally validate; this allows flexibility in the timing of circadian output signals. Phasic GABA, however, does not significantly affect molecular timekeeping. The tonic GABA signal is released when cells become very excited and depolarized; it changes the excitability of neurons in the network, can shift molecular rhythms, and affects SCN synchrony. We measure which neurons are excited or inhibited by GABA across the day and find GABA-excited neurons are synchronized by—and GABA-inhibited neurons repelled from—this tonic GABA signal, which modulates the synchrony in the SCN provided by other signaling molecules. Our mathematical model also provides an important tool for circadian research, and a model computational system for the many multiscale projects currently studying brain function.

Figure from paper:



Legend: Experimentally measured intracellular chloride is used to determine E_{GABA} for simulations, leading to predictions of strong effects of GABA signaling on cellular electrical activity rhythms. (*A*) Confocal microscopy of MQAE fluorescence in a unilateral SCN from an acute slice. (Scale bar, 100 μm.) MQAE is quenched by chloride, so areas with high fluorescence represent low intracellular chloride. Magnified images of cell bodies in dorsal, D, cells show lower fluorescence than those in ventral, V, cells. (*B*) Fluorescence values from the whole SCN slice are averaged over cell-sized regions, and (*C*) used to estimate the relative distribution of E_{GABA}. Cells with high E_{GABA} are excited by GABA, and with low E_{GABA} are inhibited by it. Note that cells are plotted on a grid for visualization purposes only and that

connectivity is determined independently of distance between cells, as described in the methods. (*D*) Estimated E_{GABA} levels across the SCN are found to be roughly normally distributed but with a clear spatial bias between the dorsal and ventral SCN. (*E*) A raster plot of simulated PER2 rhythms over 20 days for an SCN with the experimentally estimated E_{GABA} values from *C* (cells are sorted by E_{GABA}). (*F*–*H*) Circadian variation in electrical activity for sample cells with E_{GABA} values of −80 mV (*F*), −60 mV (*G*), and −32 mV (*H*), plotted as the range of voltages attained by the cells throughout the day. Circadian time is determined relative to the peak in whole SCN PER2 protein levels, which is defined to be CT12.

Role in Grant: Much of the first aim of the grant sought to determine the role of the depolarized states we had discovered in neurons. This work was proposed to be collaborative with experimentalists. Here we discovered that the role of these depolarized states was to synchronize the genetic oscillators by producing a tonic GABA signal. We also determined that this allowed the neuronal firing, which we said we would study in the grant, to continue and have the flexibility to send many neuronal signals.

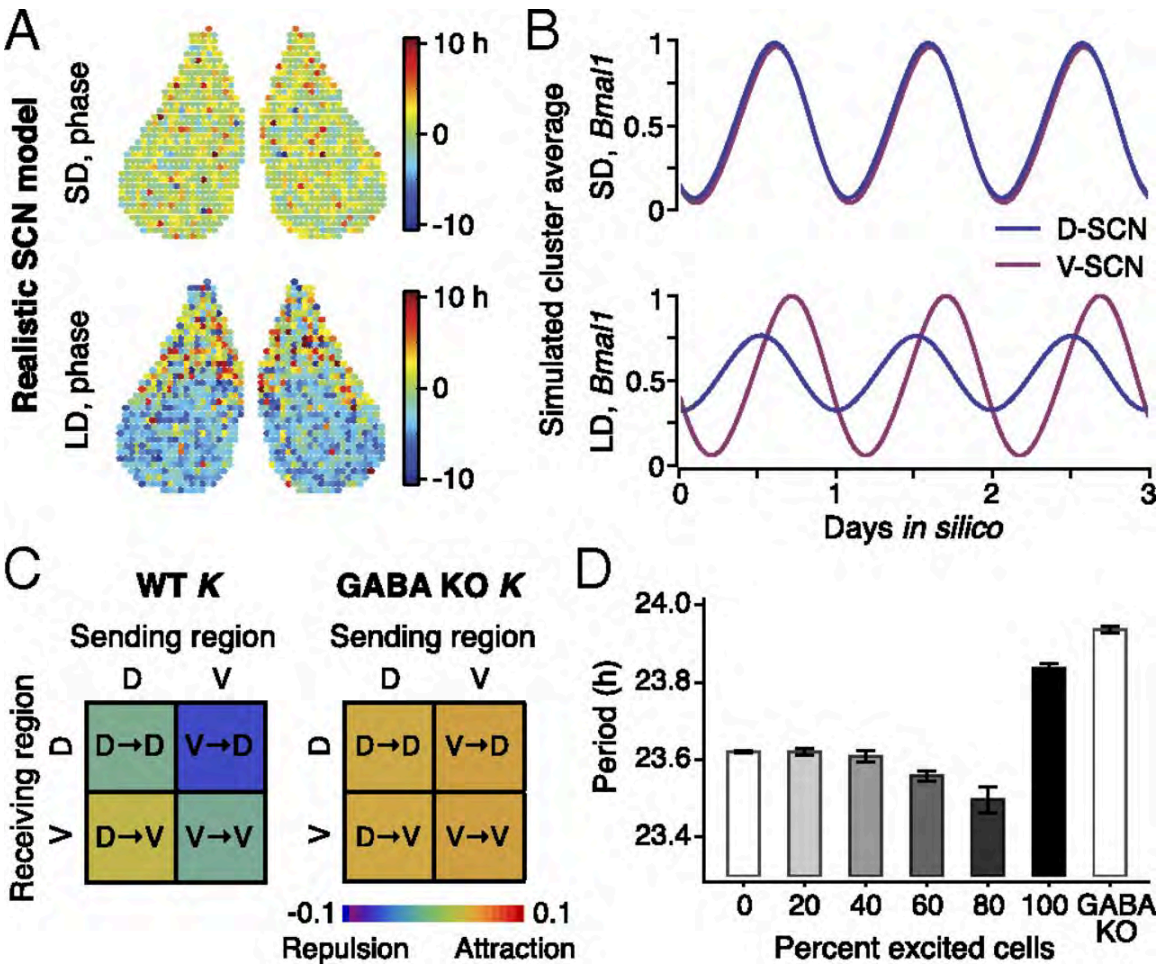
Summary of Myung J, Hong S, DeWoskin D, De Schutter E, Forger DB and Takumi T "GABA-mediated repulsive coupling between circadian clock neurons encodes seasonal time." *PNAS* 112 (2015) E3920-9.

Summary from paper: How animals track the seasons has long been a mystery. We found a mechanism that explains how day length is encoded within the neuronal network of suprachiasmatic nucleus (SCN). Using an integrated approach combining experiments and modeling, we find evidence for changes in the coupling in the SCN that divides the clock oscillations into two clusters as a function of day length. We show that asymmetric distribution of intracellular chloride across the SCN causes this coupling change. Blocking GABA or chloride import erases the oscillator organization formed by day-length entrainment. These demonstrate that coupling through GABA is a key ingredient of day-length encoding in the SCN.

The mammalian suprachiasmatic nucleus (SCN) forms not only the master circadian clock but also a seasonal clock. This neural network of ~10,000 circadian oscillators encodes season-dependent day-length changes through a largely unknown mechanism. We show that region-intrinsic changes in the SCN fine-tune the degree of network synchrony and reorganize the phase relationship among circadian oscillators to represent day length. We measure oscillations of the clock gene *Bmal1*, at single-cell and regional levels in cultured SCN explanted from animals raised under short or long days. Coupling estimation using the Kuramoto

framework reveals that the network has couplings that can be both phase-attractive (synchronizing) and -repulsive (desynchronizing). The phase gap between the dorsal and ventral regions increases and the overall period of the SCN shortens with longer day length. We find that one of the underlying physiological mechanisms is the modulation of the intracellular chloride concentration, which can adjust the strength and polarity of the ionotropic GABAA-mediated synaptic input. We show that increasing day-length changes the pattern of chloride transporter expression, yielding more excitatory GABA synaptic input, and that blocking GABAA signaling or the chloride transporter disrupts the unique phase and period organization induced by the day length. We test the consequences of this tunable GABA coupling in the context of excitation–inhibition balance through detailed realistic modeling. These results indicate that the network encoding of seasonal time is controlled by modulation of intracellular chloride, which determines the phase relationship among and period difference between the dorsal and ventral SCN.

Figure from paper:



Legend: The realistic multiscale SCN model reproduces day length-dependent reorganization of phases. (*A*) A multiscale, multicellular SCN simulation that models both electrophysiology and gene expression in each neuron faithfully reproduces emergent separation of phases between D- and V-SCN subregional oscillators under simulated LD, which is minimal under simulated SD. (*B*) The phase separation is replotted as the averages of the *Bmal1* transcript levels in D-SCN and V-SCN subregional clusters. (*C*) The estimated mean phase coupling coefficients (*K*) from the simulation recovers the asymmetric coupling motif with a repulsive coupling

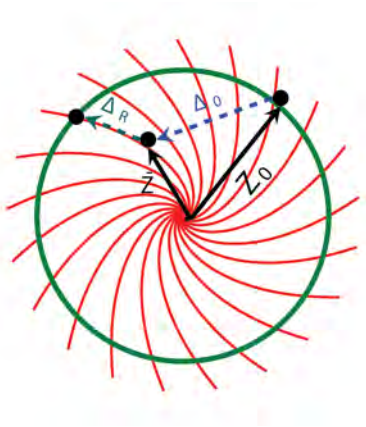
from D-SCN to V-SCN (*Left*), which disappears when GABA coupling is removed from the model parameter (*Right*) (SEM ≤0.001, n = 3 simulated SCNs). (*D*) The realistic model predicts both the shortened dorsal period owing to increased GABA excitation during LD and the lengthened period in cultured SCN during GBZ application (GABA knockout) as consequences of the change in E/I ratio.

Role in grant: This manuscript details work determining how coupled genetic and neuronal oscillators can process information. We show how the seasons can be encoded in the phase of these oscillators. This points to coupled oscillator as being a powerful tool, used in nature, to encode information.

Summary of Hannay KM, Booth V, and Forger DB "Collective phase response curves for heterogeneous coupled oscillators Phys. Rev. E 92 (2015) 022923.

Summary from paper: Phase response curves (PRCs) have become an indispensable tool in understanding the entrainment and synchronization of biological oscillators. However, biological oscillators are often found in large coupled heterogeneous systems and the variable of physiological importance is the collective rhythm resulting from an aggregation of the individual oscillations. To study this phenomena we consider phase resetting of the collective rhythm for large ensembles of globally coupled Sakaguchi-Kuramoto oscillators. Making use of Ott-Antonsen theory we derive an asymptotically valid analytic formula for the collective PRC. A result of this analysis is a characteristic scaling for the change in the amplitude and entrainment points for the collective PRC compared to the individual oscillator PRC. We support the analytical findings with numerical evidence and demonstrate the applicability of the theory to large ensembles of coupled neuronal oscillators.

Figure from paper:



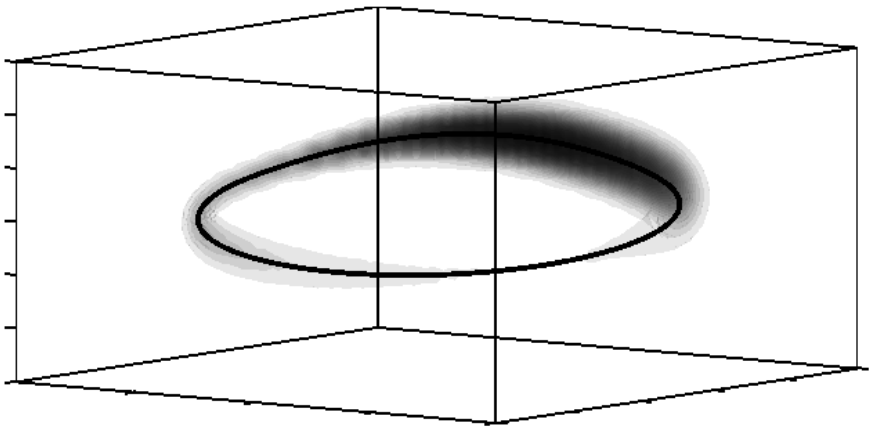
Legend: This figure shows the geometry of perturbations to a coupled oscillator system. The order parameter, measuring the degree of synchrony of the oscillators, just before the perturbation is at $\mathbf{Z_0}$. Just after the perturbation it is shifted to $\overline{\boldsymbol{Z}}$. Δ_0 tracks the shift in the mean phase that occurs in the movement from $\mathbf{Z_0}$ to $\overline{\boldsymbol{Z}}$. However, we find that an additional phase shift is observed after the stimulus is given and as the oscillator resynchronize. This is labeled Δ_R and can also be thought of as the relaxation phase shift of the collective oscillator.

Role in the grant: Aim 2 sought to determine the behavior of coupled oscillator systems. Here, we summarize these results and present a general mathematical framework for them.

Summary of Stinchcombe and Forger "A Efficient Method for Simulation of Noisy Coupled Multi-Dimensional Oscillators." Submitted to the Journal of Computational Physics

A major hurdle in the study of biological oscillators is the complexity of the models that describe the underlying biology. One could naïvely simplify the models, but this could easily cause much of the important biology to be removed. We are able to directly simulate the detailed models, but this requires special hardware (GPU) making simulation of these systems impractical for many users. Aim 2 of the grant asked us to consider this issue, but additionally consider the role of noise.

In this manuscript, we report a new methodology to simulate noisy coupled oscillators from detailed models. The general methodology takes the limit of the number of oscillators to infinity, which allows one to study a probability density function over the oscillator states. An example of this is shown below.



We then choose representative points from this probability distribution and simulate them with noise. From their collective action, the behavior of the system can be calculated. Amazingly, we find that only a low number of oscillators (e.g. < 50) need to be simulated. This represents a speed up of two orders of magnitude when compared with our original simulations of the SCN.

This method should be widely applicable in the future and are hopeful it will soon be published.

Summary of Schlizerman E, Phillips-Portillo J, Forger DB and Reppert SM to be submitted to Neuron

Monarch butterflies each year undergo one of the most amazing feats of nature when they travel from all across North America to their over wintering sites in a small region of Mexico. The ability of an insect to correctly navigate thousands of miles is of great interest to the US military as the use of unmanned vehicles continues to be a priority. Prior experimental work on this topic was funded through FA9550-10-1-0480 to the Reppert lab, the premier laboratory studying the mechanisms of monarch navigation. We sought to use this data to propose a mechanism by which visual information can be combined with an internal timekeeping mechanism to form a sun compass.

In a collaboration between the Reppert group, Eli Schlizerman at the University of Washington, we have proposed a mathematical model for the sun compass in Monarchs. This model accounts for the neurophysiology of the monarch brain, including phototransduction in the retina, and circadian timekeeping generated in the antennae. The model accurately predicts how the direction of flight would change over the day, and short-term corrections to the flight path.

The work is central to the interest to the AFOSR program on sensory information systems. It has also generated a lot of interest from the community. An editor at

Neuron requested we send our manuscript there. We plan to do so in the next week or two.

1.

1. Report Type

Final Report

Primary Contact E-mail
Contact email if there is a problem with the report.

forger@umich.edu

Primary Contact Phone Number
Contact phone number if there is a problem with the report

734-763-4544

Organization / Institution name

University of Michigan

Grant/Contract Title
The full title of the funded effort.

Understanding Synchrony and Stochasticity in Coupled Neuronal and Genetic Oscillators

Grant/Contract Number
AFOSR assigned control number. It must begin with "FA9550" or "F49620" or "FA2386".

FA9550-14-1-0092

Principal Investigator Name
The full name of the principal investigator on the grant or contract.

Daniel Forger

Program Manager
The AFOSR Program Manager currently assigned to the award

Patrick Bradshaw

Reporting Period Start Date

06/01/2014

Reporting Period End Date

05/31/2015

Abstract

Coupled biological oscillators form the basis of much decision making in humans as well as the animal world. Oscillations typically occur biochemically within a cell, or through cell signals using changes in the cells electrical activity. Here, we seek to understand these processes using mathematical modeling. The work is computational, but based on careful consideration of biological data. This allows us to derive general principles that can be widely applied to many systems, both biological and nonbiological. Our work also uses cutting edge computational techniques, which also can be widely applied. Our original proposal of two years was cut to one. Nevertheless, we have made extraordinary progress on the aims of the grant. Two papers have been published in PNAS. Additionally, another paper has appeared, and two more are in progress.

We have discovered how multiple signals can be simultaneously sent with the same signaling molecules. The basis for this was the hyperexcited states studied in Aim 1. We have discovered how a coupled oscillator system can be used to encode patterns of light indicating the season also based on these hyperexcited states. We have developed general principles for how a coupled oscillator system responds differently to light than if the individual elements were uncoupled. Additional work not yet published has uncovered new tools to rapidly simulate coupled noisy oscillator systems. This later work comes directly

from Aim 2. Additionally, fulfilling an Air Force need, we have used our work to understand principles of monarch butterfly navigation.

We remain thankful to AFOSR for the opportunity to perform this research.

Distribution Statement

This is block 12 on the SF298 form.

Distribution A - Approved for Public Release

Explanation for Distribution Statement

If this is not approved for public release, please provide a short explanation. E.g., contains proprietary information.

SF298 Form

Please attach your SF298 form. A blank SF298 can be found here. Please do not password protect or secure the PDF The maximum file size for an SF298 is 50MB.

AFD-070820-035.pdf

Upload the Report Document. File must be a PDF. Please do not password protect or secure the PDF . The maximum file size for the Report Document is 50MB.

finalreport0092.pdf

Upload a Report Document, if any. The maximum file size for the Report Document is 50MB.

Archival Publications (published) during reporting period:

DeWoskin D, Myung J, Belle MD, Piggins HD, Takumi T and Forger DB “Distinct roles for GABA across multiple timescales in mammalian circadian timekeeping” PNAS 112 (2015) E3911-9.

Myung J, Hong S, DeWoskin D, De Schutter E, Forger DB and Takumi T “GABA-mediated repulsive coupling between circadian clock neurons encodes seasonal time.” PNAS 112 (2015) E3920-9.

Hannay KM, Booth V, and Forger DB “Collective phase response curves for heterogeneous coupled oscillators Phys. Rev. E 92 (2015) 022923.

Changes in research objectives (if any):

None

Change in AFOSR Program Manager, if any:

None

Extensions granted or milestones slipped, if any:

None

AFOSR LRIR Number

LRIR Title

Reporting Period

Laboratory Task Manager

Program Officer

Research Objectives

Technical Summary

Funding Summary by Cost Category (by FY, $K)

	Starting FY	FY+1	FY+2
Salary			
Equipment/Facilities			
Supplies			
Total			

Report Document

Report Document - Text Analysis

Report Document - Text Analysis

Appendix Documents

2. Thank You

E-mail user

Aug 31, 2015 13:15:55 Success: Email Sent to: forger@umich.edu